PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2007/013700	11.06.2007	12.06.2006

International Patent Classification (IPC) or both national classification and IPC
INV. C12Q1/68 H01L29/06

Applicant
PRESIDENT AND FELLOWS OF HARVARD COLLEGE

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	See form PCT/ISA/210	Aslund, Fredrik Telephone No. +31 70 340-4393

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☒ on paper

      ☒ in electronic form

   c. time of filing/furnishing:

      ☒ contained in the international application as filed.

      ☒ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 30-85

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 30-85

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-29

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	28, 29
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-29
Industrial applicability (IA)	Yes:	Claims	1-29
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item IV.

The separate inventions/groups of inventions are:

Invention 1: Claims 1-29
A method, comprising an act of: determining a binding constant and/or a dissociation rate constant between a nucleic acid or an analyte and a nanoscale wire having immobilized relative thereto a binding partner of the nucleic acid.

Invention 2: Claims 30-41
A method, comprising acts of: diffusing at least a portion of a metal into a first portion of a nanoscale wire but not into a second portion of the nanoscale wire; and immobilizing a reaction entity to a second portion of the nanoscale wire.

Invention 3: Claims 42-53, 64-77
An article, comprising: a nanoscale wire comprising a first portion comprising a metal silicide; and a reaction entity immobilized relative to a second portion of the nanoscale wire having a composition different from the first portion. Furthermore, An article, comprising: a nanoscale wire comprising a first portion comprising a metal silicide; and a second portion having a composition different from the first portion, wherein the second portion has a greatest dimension no greater than about 100 nm. Furthermore,
An article, comprising: a nanoscale wire comprising a first portion and a second portion, the first portion having a binding partner immobilized relative thereto, the second portion being free of the binding partner.

Invention 4: Claims 54-63
A method, comprising acts of: providing a bulk metal adjacent a semiconductor wire; and diffusing at least a portion of the bulk metal into at least a portion of the semiconductor wire in a longitudinal direction along the semiconductor wire for a distance of at least about 10 nm.

Invention 5: Claims 78-80
A solution, comprising:
an analyte; and a nanoscale wire comprising a first portion and a second portion, the

second portion having immobilized relative thereto a binding partner to the analyte and the first portion free of the binding partner, wherein the analyte has a Debye screening length greater than the greatest dimension of the second portion of the nanoscale wire.
Invention 6: Claims 81-85
A method, comprising acts of: determining a number of mismatches between an analyte nucleic acid and a binding partner. nucleic acid immobilized relative to a binding partner of the nucleic acid.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

1. Reading the claims in the light of the description the technical problem to be solved could initially be considered to be the provision of "A method, comprising an act of: determining a binding constant and/or a dissociation rate constant between a nucleic acid or an analyte and a nanoscale wire having immobilized relative thereto a binding partner of the nucleic acid" and methods of diffusing a metal into a nanoscale wire or a semiconductor wire and furthermore articles and solutions comprising nanoscale wires and yet furthermore methods of determining mismatches between an analyte nucleic acid and a binding partner. These methods and products have nothing in common.

2. In view of the absence of a common concept and since no further special technical feature (structural or functional) linking the different inventions of the present application could be found, the application is considered to provide the separate inventions listed above.

3. Due to the fact that: I) The no common concept could be found, ii) essential differences exist between the inventions listed above, iii) no other technical features can be distinguished which could be regarded as special technical features in the sense of Rule 13.2 PCT, the ISA is of the opinion that there is no single inventive concept underlying the claimed inventions of the present application in the sense of Rule 13.1 PCT. Consequently there is lack of unity and the different inventions are formulated as the different subjects on the communication pursuant to Art. 17(3)(a)PCT. Therefore, and bearing in mind that every one of the inventions distinguished above requires a separate search in the appropriate databases and classified documentation, the International

Search Authority considers that the PCT guidelines 10.64-10.65 regarding complete search with negligible additional work is not applicable. Thus, since only the first invention as defined above has been fully searched, this opinion is restricted accordingly.

Re Item V.

Regarding Invention 1:

Citations:

D1: HAHM J ET AL: "Direct Ultrasensitive Electrical Detection of DNA and DNA Sequence Variations Using Nanowire Nanosensors" NANO LETTERS, ACS, WASHINGTON, DC, US, vol. 4, no. 1, 12 September 2003 (2003-09-12), pages 51-54, XP007903534 ISSN: 1530-6984

D2: LI Z ET AL: "Sequence-Specific Label-Free DNA Sensors Based on Silicon Nanowires" NANO LETTERS, ACS, WASHINGTON, DC, US, vol. 4, no. 2, 8 January 2004 (2004-01-08), pages 245-247, XP002407747 ISSN: 1530-6984

D3: YI CUI ET AL: "Nanowire nanosensors for highly sensitive and selective detection of biological and chemical species" SCIENCE, WASHINGTON, DC, vol. 293, no. 5533, 17 August 2001 (2001-08-17), pages 1289-1292, XP002264236 ISSN: 0036-8075

Novelty

Independent Claim 28 concerns:
"A method, comprising an act of: determining a binding constant and/or a dissociation rate constant between an analyte and a nanoscale wire having immobilized relative thereto a binding partner of the nucleic acid."
D3 (pages 1291-1292) calculates dissociation constants between analytes a binding partner immobilized on a nanowire. Hence, claims 28, 29 lack novelty.

Inventive step

The closest state of the art D1 (or D2) discloses SNP detection wherein a binding partner nucleic acid has been immobilized on a nanowire (Figure 1). Independent claims 1 differs

from D1 in that a binding constant and/or dissociation constant is determined.
The problem to be solved can thus be seen as further methods of nucleic acid analysis using nanowires.
The proposed solution is the inclusion of a step for determination of a binding constant and/or dissociation constant.
D3 (pages 1291-1292) calculates dissociation constants between analytes a compound immobilized on a nanowire. Thus, the data analyzed in D3 is similar to the data in D1 (or D2) but referring to interactions between compound other than nucleic acids.
It would be an obvious standard alternative to a person skilled in the art to use the methods of D3 to calculate dissociation constants for the nucleic acid analysis of D1 (or D2). Hence, an inventive step is denied for claim 1. None of the dependent claims appear to disclose subject-matter on which an inventive step could be based.

It can also be point out that the step of determining dissociation constants from nanowire measurements of interactions between two nucleic acids is hardly technical in nature. D1, D2 successfully discriminates between mismatches without such calculations. Thus, in addition to the above reasoning, invention 1 is also lacking an inventive step since no technical effect is association with the step of calculating a binding constant and/or dissociation constant.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003